II. Reissue Declaration (37 C.F.R. §1.175)

The filed reissue declaration was alleged to be defective. As suggested in Paper No. 2, a substitute declaration containing the recommended wording of MPEP 1414, Section III is submitted herewith.

III. Patent Ownership (37 C.F.R. §3.73(b))

The filed "Petition and Offer to Surrender Original Patent Grant" was alleged to be defective. As suggested in Paper No. 2, a completed "CERTIFICATE UNDER 37 C.F.R. §3.73(b)" is submitted herewith.

IV. New Matter (35 U.S.C. §112, first paragraph)

Claims 21-42 were rejected under 35 U.S.C. §112, first paragraph, because they allegedly "contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention". Specifically, it was asserted that claims 21-42 are drawn to a "secondary amplification" to the Polymerase Chain Reaction (PCR) amplification method, and that the originally filed specification does not describe PCR coupled to the "secondary amplification". It is further asserted that the specification describes Strand Displacement Amplification (SDA) coupled to the "secondary amplification", and that SDA is a materially different and distinct amplification method from PCR. In support of this allegation, reference was made to the first full paragraph of column 2 of the present reissue application.

Applicants respectfully disagree with the assertion that the coverage of PCR and other amplification methods by new claims 21-42 constitutes new matter. The original specification contains numerous passages indicating the applicability of the invention with amplification methods in addition to SDA. For example:

(1) The present invention is described generically as "a primer-based amplification detection method in which the need for a second amplification reaction is eliminated." (Column 3, lines 50-52).

(2) Similarly, the originally filed specification generically defines an amplification primer as "a primer for amplification of a target sequence by primer

extension." (Column 4, lines 1-2). The genericness of this description is confirmed by the next sentence which exemplifies an SDA amplification primer by further characterization as a species of the generic amplification primer.

(3) Extension products are also defined generically as "nucleic acids which comprise a primer and a newly synthesized strand which is the complement of the target sequence downstream of the primer binding site." (Column 4, lines 28-31). This definition also continues to generically state that "[e]xtension products result from hybridization of a primer to a target sequence and extension of the primer by polymerase using the target sequence as a template." (Column 4, lines 31-33).

(4) The terms target or target sequence are defined generically as "produced in the amplification reaction" (emphasis added). (Column 4, lines 46-52).

(5) The amplification products are similarly generically defined, and are specified as "including intermediates of the amplification reaction" (emphasis added). (Column 4, line 63 - Column 5, line 2).

(6) In the discussion of methods for detection of a signal primer, it is noted that "[a]ll of these methods are useful in the present invention and one skilled in the art can routinely select appropriate methods for use in any particular amplification assay system" (emphasis added). (Column 6, lines 21-24).

Furthermore, the citation in Paper No. 2 of the contrast of PCR and SDA at column 2, first full paragraph, is supportive of the generic disclosure of the originally filed specification. In context, this passage is found in the Background of the Invention section, and is presenting the problems of primer-based methods for detecting PCR amplification products. This passage is then followed by a paragraph which describes the predicted additional problems of a primer-based method for detecting SDA amplification products ("even higher levels of background signal" as compared to PCR). (Column 2, lines 49-62). Thus, consistent with the generic

description and definitions referenced above, the invention was intended to address problems of primer-based methods for detecting amplification products, and to the extent that the predicted greater problems of SDA are addressed, the lesser problems of PCR are similarly addressed.

Moreover, the cited discussion of the undesirability of high levels of background signal in Paper No. 2 further supports a generic, as well as a specific, inclusion of PCR in the originally filed specification. Particularly, at the end of the passage cited in Paper No. 2, it is stated that "[t]he present invention therefore greatly simplifies the procedures for primer-based detection methods, which previously relied on two consecutive amplification reactions to attain high sensitivity and specificity, the second reaction being performed with internally nested signal-generating amplification primers." (Column 6, lines 35-41). This passage is firstly generic to primer-based detection methods, and secondly directly ties back to the discussion of problems of primer-based methods for detection of PCR amplification products in the Background of the Invention Section.

Thus, it is respectfully submitted that new claims 21-42 do not constitute the addition of new matter to the present reissue application.

V. Enablement (35 U.S.C. §112, first paragraph)

Claims 21-42 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, it was alleged that in a PCR reaction, undesirable high levels of background signal will be present, because signal primers have all of the essential characteristics of amplification primers and thus will participate in the nucleic acid amplification reaction. It is then alleged that the specification lacks examples and guidance explaining how to use signal primers which participate in the amplification reaction while avoiding the high levels of background signal.

It is respectfully submitted that the rejected claims are fully enabled, because the genericness of the claims is embodied in the fact that the signal primer is situated downstream of the amplification primer. Also, because of this configuration of signal primer and amplification primer, the alleged undesirable high levels of background signal are not manifest in a primer based amplification method.

Specifically, in such a configuration, any undesirable level of background signal will only be present upon the simultaneous mispriming of both the amplification primer and the signal primer. Even if such a simultaneous dual mispriming event occurs, the labeled signal primer (the only component capable of contributing to background signal) will only be a part of a linear extension reaction, which should not produce background signal at a level comparable to the desired target signal.

As noted in the original specification, "[h]igh levels of background signal are believed to be due to non-specific priming and subsequent amplification of spuriously primed non-target DNA" (emphasis added). (Column 6, lines 33-36). Also, as noted in the original specification, a single mispriming event "is comparatively rare", and thus "is detectable only after subsequent amplification of the misprimed sequence" (emphasis added). (Column 3, lines 57-59). Therefore, the simultaneous dual mispriming of an amplification primer and a signal primer downstream therefrom necessary for the displacement and linear extension of misprimed signal primer product will be an extremely rare occurrence. Furthermore, the original specification allows for some linear accumulation of signal primer product. (Column 5, lines 10-14).

Therefore, it is respectfully submitted that claims 21-42 are fully enabled by the original specification.

VI. Anticipation (35 U.S.C. §102(b)

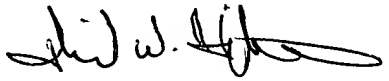
Claims 43-50 were rejected under 35 U.S.C. §102(b) as being anticipated by Mullis et al., U.S. Patent No. 4,683,195 (7/1987) ("Mullis"), or Urdea, U.S. Patent No. 5,200,314 (4/1993) ("Urdea").

However, it is respectfully submitted that neither Mullis nor Urdea disclose or suggest the feature of the claimed signal primer which is responsible for its unique properties. Specifically, the properties of the claimed signal primer include its ability to hybridize to a target sequence at a position downstream of the position where a nucleic acid amplification primer hybridizes to the target sequence. Neither Mullis nor Urdea describe primers having this hybridization property.

VII. Conclusions

In view of the remarks above, and the ancillary documents submitted herewith, the present reissue application is believed to be in condition for allowance.

Respectfully submitted,



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